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# Photodynamic Therapy of Primary Nonmelanomatous Skin Tumours of the Head and Neck

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***Background and Objectives:*** **Nonmelanomatous skin tumours are the most frequent tumours in the white population and mainly caused by cumulative exposure to ultraviolet B radiation. On account of this origination about 80% of all nonmelanomatous skin tumours are located on the arms or the head and neck. Standard treatment for most tumours is surgical resection, with often only moderate cosmetic outcome.**
***Study Design/Materials and Methods:*** **In a prospective clinical trial the effect of photodynamic therapy on primary nonmelanomatous skin tumours of the head and neck (basal cell cancer, squamous cell cancer) was tested. In this study Foscan (meta-Tetrahydroxyphenylchlorin/mTHPC), a systemic photosensitizer of the second generation, was applied. Patients were injected 0.15 mg/kg or 0.10 mg/kg Foscan intravenously 96 hours prior to laser light exposure. Light was delivered via fibres by an argon-dye laser at 652 nm, 100 mW/cm$^2$ and a light dose of 5–20 J/cm$^2$.**
***Results:*** **Eighteen patients with a total of 97 nonmelanomatous skin tumours and a mean follow up of 15 months (ranging 3–24 months) were treated. Within several days tumour necrosis appeared followed by wound healing within 4–8 weeks, leaving only minor scars behind. Ninety tumours (92.7%) showed a complete response with an excellent cosmetic outcome and only seven tumours responded by partial success due to low light dosage. The cosmetic outcome was very good and the therapy was supported by a high degree of patient satisfaction.**
***Conclusion:*** **By choosing the correct drug and light dosage, a selective tumour necrosis can be obtained. Photodynamic therapy (PDT) using Foscan seems to be a promising new and safe treatment modality for the treatment of primary nonmelanomatous skin tumours of the head and neck that can substitute surgical therapy, offering an even better cosmetic outcome. Lasers Surg. Med. 25:60–68, 1999.** © 1999 Wiley-Liss, Inc.

**Key words:** **nonmelanomatous skin tumour; head and neck; photodynamic therapy; mTHPC; Foscan**

## INTRODUCTION

More than one third of all cancers in the United States are nonmelanomatous skin cancers [1]. Exposure to sunlight is the principle cause for

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this kind of tumour. For Caucasians their incidence is strongly associated with age and cumulative ultraviolet B radiation [2,3]. However exposure to chemical carcinogens, ionizing radiation, chronic ulceration, immunsuppression, or genetic defects also account for these tumours. Due to their genesis, most nonmelanomatous skin tumours are located in sun-exposed skin parts. Therefore 80% of the squamous cell cancers and basal cell carcinomas of the skin are found on the arms or the head and neck [2]. Even after a curative therapy the risk of subsequent skin tumours is high [4]. About 50% of the patients with a history of nonmelanomatous skin cancer will develop a new skin cancer at another site within the first five years independent of the primary therapy [5]. In patients with a genetic defect, immunsuppression or chemical induced tumours, the risk of subsequent tumours can be even higher. These patients may suffer simultaneously from more than one and up to several dozen skin tumours or premalignant skin lesions at various sites, not only limited to the arms, head, or neck. On account of the link between skin tumours and ultraviolet B light exposure and the changing leisure activities in western societies, nonmelanomatous skin tumours are an emerging problem in dermatology as well as in plastic and reconstructive surgery.

These skin tumours can be treated by surgical and nonsurgical methods. Dependent on tumour location, size, type (primary or recurrence), histology, patient morbidity, and preference different treatment methods like surgical excision, Mohs' micrographic surgery, cryosurgery, curettage, laser ablation, or radiation therapy can be applied [3]. Up to now surgery has been the mainstay of therapy for nonmelanomatous skin tumours. In patients with large or multifocal tumours, a good cosmetic outcome after surgery can be difficult to obtain. This is especially true for lesions on the face or in patients with multilocalized lesions, where primary wound closure after surgery can be difficult to achieve, requiring reconstruction by plastic surgery, e.g., local skin flaps, skin graft, or healing by second intention.

The selective uptake and retention of a systemically applied photosensitizer in tumour tissue is the basic principle of photodynamic therapy (PDT) [6,7]. After intratumoural uptake, intracellular activation of the photosensitizer by light of a specific wavelength results either in the formation of radical products (type I mechanism) or intracellular singlet oxygen (type II mechanism), which cause cell death by vascular shut down mechanisms and intracellular oxidation. PDT has been applied to the treatment of tumours in the oesophagus, bronchus, bladder, skin, as well as other sites. Skin tumours seem to be an ideal indication for PDT. Due to good access, skin can be illuminated directly and the follow-up and therapy success control is much easier than in any other organ.

The aim of this clinical study is to investigate if PDT with Foscan (meta-Tetrahydroxyphenylchlorin/mTHPC) is an effective treatment modality for primary nonmelanomatous skin tumours of the head and neck and whether a satisfying cosmetic result can be obtained. This is the first preliminary clinical report about the application of Foscan for the treatment of skin tumours in humans.

## MATERIALS AND METHODS

This study was approved by the local ethic committee. All patients were informed about the investigative nature of the study and gave their written informed consent prior to the treatment.

### Patients and Indications

Patients with histologically proven basal cell cancer (BCC) or squamous cell cancer (SCC) of the skin could enter the study. All treated lesions were biopsied prior to the treatment. In patients with a multilocalized disease, like Gorlin-Goltz syndrome, only one or two lesions were biopsied prior to the treatment. All other lesions were diagnosed by an experienced dermatologist.

### Photosensitizer Dosage and Application

Eight patients received 0.10 mg/kg and 10 patients received 0.15 mg/kg Foscan (Scotia QuantaNova, England) by intravenous injection 96 hours prior to PDT.

### Light Source and Illumination

All lesions were illuminated superficial with 652 nm red light delivered by an argon-dye laser system (Spectra Physics, Mountain View) using a fibre with a microlens applicator. The light power density was 100 mW/cm$^2$. Depending on tumor depth and histology a light dose of 5, 10, 15, or 20 J/cm$^2$ was chosen. Superficial lesions with a clinical depth of less than 3 mm received 5 or 10 J/cm$^2$ whereas lesions with more than 2 mm of depth received 15 J/cm$^2$. All squamous cell cancers, except one very superficial tumor (5 J/cm$^2$), were treated by 20 J/cm$^2$. For all lesions a safety mar-

**TABLE 1. Patients Treated by Foscan Mediated PDT[a]**

| Pat | Lesion no. | Histology | Photosensitizer dosage (mg/kg) | Light dosage ($J/cm^2$) | Recurrence | Cosmetic outcome |
|---|---|---|---|---|---|---|
| 1 | 19 | 19 × BCC | 0.10 | 5–10 | 0 | 6 × good<br>13 × average |
| 2 | 3 | 3 × BCC | 0.10 | 5–10 | 0 | 2 × very good<br>1 × average |
| 3 | 26 | 26 × BCC | 0.10 | 5–10 | 3 | 18 × very good<br>7 × good<br>1 × average |
| 4 | 22 | 22 × BCC | 0.10 | 10 | 0 | 18 × very good<br>4 × average |
| 5 | 1 | 1 × BCC | 0.10 | 10 | 0 | 1 × very good |
| 6 | 1 | 1 × BCC | 0.10 | 10 | 1 | 1 × very good |
| 7 | 1 | 1 × BCC | 0.10 | 10 | 0 | 1 × average |
| 8 | 1 | 1 × BCC | 0.10 | 15 | 0 | 1 × poor |
| 9 | 1 | 1 × BCC | 0.10 | 15 | 1 | 1 × good |
| 10 | 9 | 9 × BCC | 0.15 | 5–10 | 2 | 8 × very good<br>1 × poor |
| 11 | 1 | 1 × BCC | 0.15 | 10 | 0 | 1 × poor |
| 12 | 1 | 1 × BCC | 0.15 | 15 | 0 | 1 × very good |
| 13 | 1 | 1 × BCC | 0.15 | 15 | 0 | 1 × good |
| 14 | 1 | 1 × BCC | 0.15 | 15 | 0 | 1 × poor |
| 15 | 5 | 5 × SCC | 0.15 | 20 | 0 | 2 × very good<br>3 × good |
| 16 | 2 | 2 × SCC | 0.15 | 20 | 0 | 2 × very good |
| 17 | 1 | 1 × SCC | 0.15 | 20 | 0 | 1 × average |
| 18 | 1 | 1 × SCC | 0.15 | 5 | 0 | 1 × very good |

[a]BCC = basal cell cancer; SCC = squamous cell cancer.

gin of 5 mm beyond the macroscopical tumor borders was included into the irradiation field. Details on patient data and treatment parameters are listed in Table 1.

### Light Precaution

Due to systemic skin photosensitivity after the intravenous injection of the photosensitizer, every patient had to stay clear from bright light for two weeks after injection. Within the first 24 hours patients had to remain indoors in a semidarkened room after which a gradual return to unrestricted light exposure over two weeks was recommended. During the period of systemic photosensitivity, light dosimeters were handed to the patients for self-control of light exposure.

### Follow-up

All lesions were examined regularly for any sign of remaining tumour by clinical examination. Suspicious lesions were biopsied for histological diagnosis. In patients with squamous cell cancer all lesions were biopsied three months after PDT and the regional lymph nodes of the neck were checked for any sign of metastasis by clinical examination and by ultrasound every three months thereafter.

Tumour response to the treatment was evaluated as complete response (CR = no evidence of tumour), partial response (PR = more than 50% reduction in size), and no response (NR = tumour reduction less than 50% or tumour progression).

The cosmetic outcome was evaluated three months after PDT. The evaluation was made by two physicians and quantified by the following scoring: 1 = very good (scar absent or barely present), 2 = good (slight scar visible but cosmetically acceptable), 3 = average (moderate scar clearly visible, no surgical revision necessary), 4 = poor (distinct scar that has to be corrected).

## RESULTS

A total of 14 patients with 88 BCC and four patients with 9 SCC of the head and neck have been treated so far. During laser treatment some patients felt a mild burning sensation within the treatment field, which did not require pain medication or local anaesthesia. Immediately after PDT no skin reaction of the lesion or the surrounding normal tissue could be seen. Within 24 hours all lesions showed an erythema with a mild edema and serum effusion that lasted for 2–4

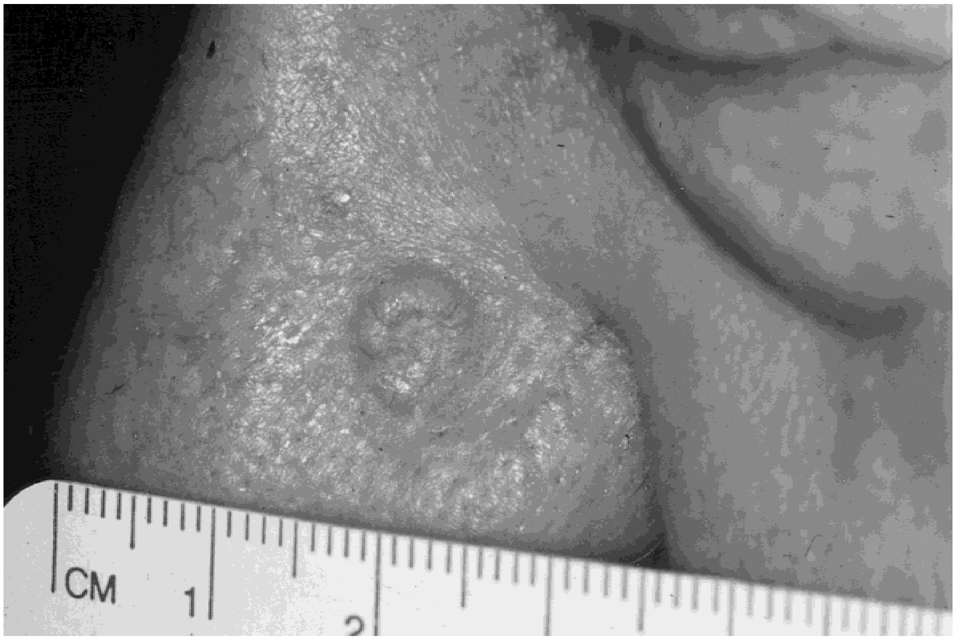


Fig. 1. Basal cell cancer at the nose prior to PDT.

days. Tissue reaction within the treatment field could be sorted into two groups:

In lesions treated with 5 or 10 J/cm$^2$ a very selective tumour necrosis appeared within two days (Figs. 1–3). The adjacent normal tissue showed a moderate erythem reaction, which disappeared within two weeks leaving normal skin behind. The necrotic tumour was replaced by normal tissue or a flat scar. Healing was completed within 4–6 weeks and all lesions healed without any or only minor signs of scarring. Indeed some could not be identified exactly any more after several months and some showed even hair regrowth. The mean cosmetic score for this low light energy group was 1.7 (SD = 0.9).

Lesions treated with 15 or 20 J/cm$^2$ showed a

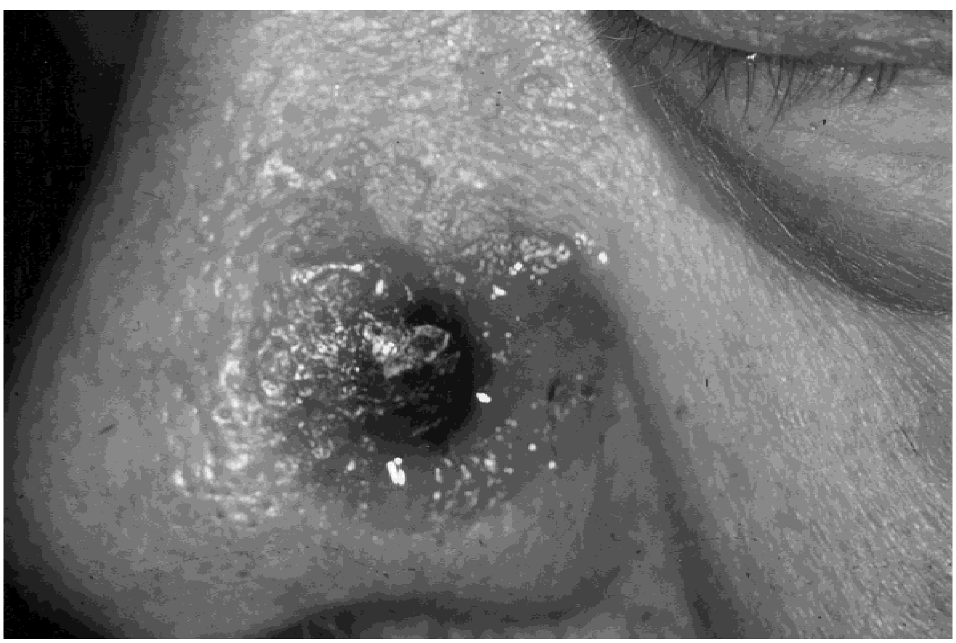

Fig. 2. Basal cell cancer at the nose two days after PDT (0.10 mg/kg Foscan; 100 mW/cm$^2$; 10 J/cm$^2$). Selective tumour necrosis.

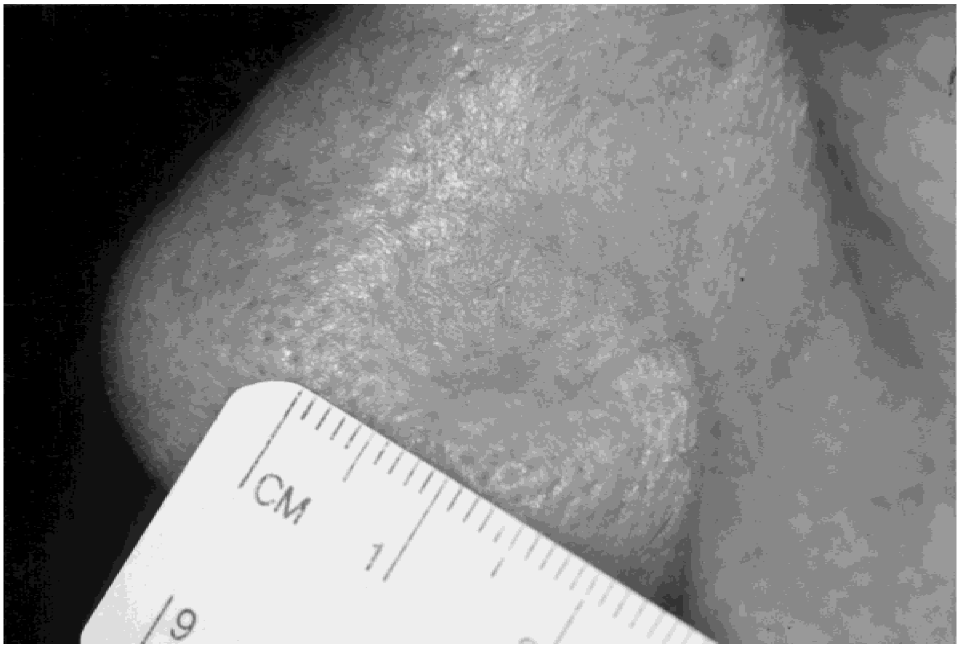


Fig. 3. Basal cell cancer at the nose 12 months after PDT. No remaining tumour.

less selective reaction (Fig. 4–6). In both drug groups the tumour as well as the adjacent normal tissue within the treatment field became necrotic within one week. But still the necrosis depth within the tumour area was deeper than in the adjacent normal tissue. This could be seen when the superficial necrosis of the treatment field was removed or felt off four weeks after PDT. At this time, the adjacent normal tissue within the treatment field was nearly completely healed whereas within the tumour area a deep necrosis was still visible. Subsequently nearly all lesions healed within 6–8 weeks. The cosmetic outcome was not quite as good as in the low light dosage group with

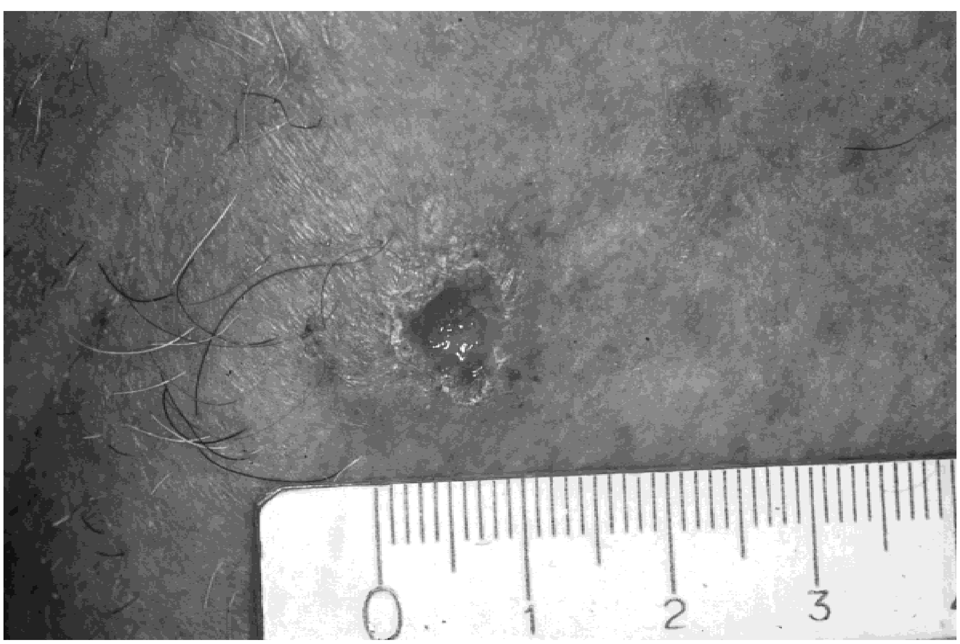


Fig. 4. Squamous cell cancer left neck prior to PDT.


Fig. 5. Squamous cell cancer left neck after PDT (0.15 mg/kg Foscan; 100 mW/cm$^2$; 20 J/cm$^2$). Less selective tumour necrosis.

a cosmetic score of 2.0 (SD = 1.0). All patients were satisfied with the treatment and the cosmetic outcome.

The complete response rate for BCC was 92% (81 lesions) with a mean follow-up of 13.9 months (3–22 months). Only seven BCC lesions (8%) showed a partial response with a reduction of tumor size by more than 50%. All of them were treated with the low light dosage of 5 or 10 J/cm$^2$ and a drug dosage of 0.10 respectively 0.15 mg/kg. All SCC (100%) showed a complete response after PDT with a mean follow up of 20 months (8–24 months). Lymph node metastasis were not found. No local wound infection occurred and no antibi-

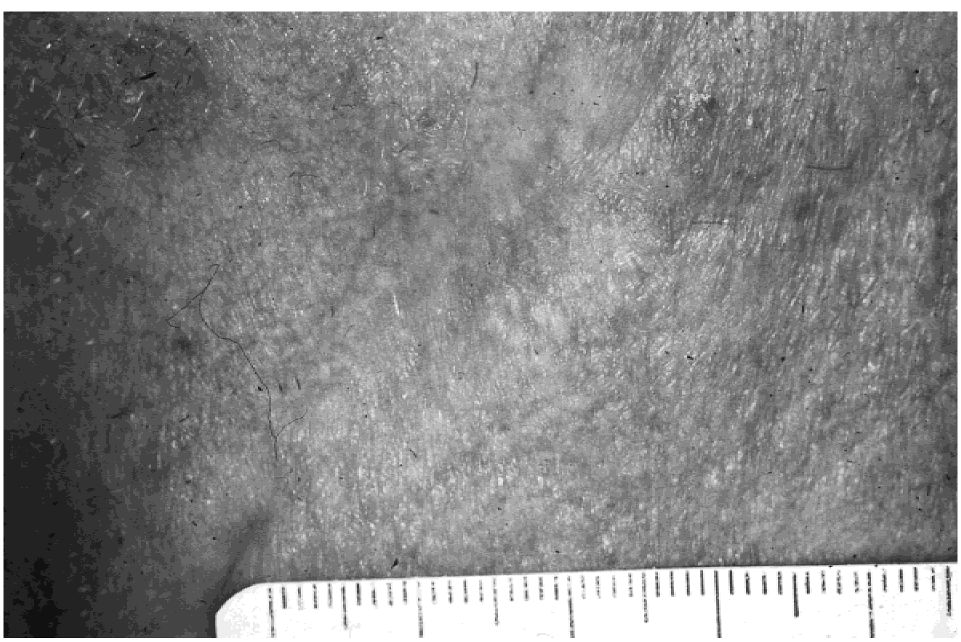

Fig. 6. Squamous cell cancer left neck 18 months after PDT. No remaining tumour.

otics nor pain medication was needed. For local wound care frequent application of a moisturizing cream was recommended.

Only very few side effects were recorded. One patient suffered from a mild sunburn and swelling after being exposed to bright sunlight 10 days after the injection of 0.15 mg/kg Foscan. Another patient suffered from a severe sunburn after walking in the bright sunlight for about one hour, 36 hours after the injection of 0.10 mg/kg Foscan. Within 24 hours thereafter she developed superficial skin necrosis and blisters on her forehead and both hands. These skin reactions healed without any scars or dysfigurations and only a mild hyperpigmentation on both hands persisted for up to three months.

## DISCUSSION

There are several previous reports about the clinical application of PDT using aminolevulinic acid (ALA) or porphyrin derivates (Photofrin, BPD) for the treatment of skin tumours [8,9]. So far various drug and light dosage combinations have been used. A wide range of tumour response rates is notified, which vary by applied photosensitizers, drug and light dosage, tumour histology, and localization.

ALA, a topical applicable photosensitizer that does not cause systemic photosensitivity was successfully employed in numerous clinical studies [10–13]. But due to its limited penetration capability through the stratum corneum the use of ALA is restricted to superficial lesions not thicker than 1–2 mm [14]. Therefore nodular BCC or any deeper lesions can not be treated with ALA. Also, the therapeutic outcome can not be predicted as being dependent to the penetration capability of ALA at the tumour surface and the ratio of protoporphyrin IX synthesis, the photoactive compound, within the tumour cells. Furthermore, patients report a severe burning sensation during light illumination, which can prevent the use of ALA, especially in treating multilocalized lesions.

There are some reports about the clinical application of intravenously administered photosensitizers for the treatment of primary skin tumours and metastatic skin diseases [15–32]. In using intravenously applied photosensitizers, drug accumulation is not limited to the superficial areas of the tumour as it is for ALA [10–14]. Instead the therapy depth depends only on the light penetration capability into human tissue, which is dominated by the activation wavelength and optical properties of the illuminated tissue [33]. For hematoporphyrin derivatives, activated at 630 nm, a maximum therapy depth of 5 mm into the skin can be expected. For nearly all studies on intravenous photosensitizers for PDT of skin tumours, hematoporphyrin derivatives (HPD, DHE, Photofrin) photosensitizers of the first generation, were applied. Various drug and light dosage combinations had been used ranging from 0.5–5 mg/kg and 25–288 J/cm$^2$. The clinical results of these studies are difficult to compare due to the various histological diagnosis as the distinguish treatment parameters [15–32]. Therefore a wide range of tumour response rates between 0–100% is notified, which varies by tumour histology and tumour location. But there is a clear tendency that by reducing the drug dosage and increasing the light energy a better selective response and better cure rate can be obtained [32]. Therefore most investigators reported satisfying response rates and good cosmetic results for superficial and nodular BCC. But PDT seems not to be suitable for the treatment of morphoeic BCC [8].

There are very few reports about the PDT of SCC. Most of them have shown good clinical results with a complete response rate of up to 100%. Only the results of Pennington et al., who have used extremely low doses of light, were disappointing [26].

Benzoporphyrin derivate (BPD), a photosensitizer of the second generation, is the only other systemical photosensitizer besides hematoporphyrin derivates that has been used for the treatment of skin tumours so far [34]. By treating 27 patients with 107 primary nonmelanomatous skin cancers and skin metastasis at various drug and light doses, a complete response rate of 57% and a partial response rate of 22% with a good cosmetic outcome could be obtained.

There are a variety of other treatment methods for nonmelanomatous skin tumours like surgical excision, curettage and electrodesiccation, radiotherapy, cryotherapy, non-Mohs' modalities, and Mohs' micrographic surgery [3]. Many of these have shown excellent response rates for the treatment of single lesions. But most of them are poorly suited for the treatment of multilocalized lesions or large areas of tumours.

The reason for the very reserved clinical application of intravenously administered photosensitizers in skin PDT might be the long lasting systemic photosensitivity of the patients. Due to the intravenous application of the drug a systemical photosensitivity of the patient occurs that forces

the patient to stay indoors, out of bright day light for up to several weeks, depending on the photosensitizer and the drug dosage.

Common to ALA and hematoporphyrin derivatives is a high light dose needed for the activation of the photosensitizer, which causes treatment times of up to 20 minutes per lesion. Especially in patients with multilocalized tumours, the overall treatment can last for several hours.

Foscan, a systemic photosensitizer of the second generation used in this study is characterized by some major improvements. By using a longer activation wavelength for Foscan (652 nm), a better tissue penetration and a therapeutic effect of up to 10 mm depth can be achieved. Therefore using Foscan mediated PDT, also nodular skin tumours can be treated.

The low activation energy of Foscan accounts for a much shorter treatment time of only 100–200 seconds per lesion. The shorter treatment time and the lack of pain facilitates the treatment of multilocalized skin tumours. By our own experience we were able to treat a maximum of 83 BCCs at the trunk of a patient with Gorlin-Goltz syndrome within one session (data not listed). After intravenous application Foscan causes a significant shorter period of photosensitization, which lasts only for two weeks. This makes PDT with Foscan more convenient than with most other photosensitizers and Foscan mediated PDT of nonmelanomatous skin tumours can be performed on an outpatient basis.

The validation of the cosmetic outcome is rather difficult. By our own subjective evaluation, lesions treated by 10 J/cm$^2$ or less, showed a slightly better cosmetic outcome than lesions treated by 15 J/cm$^2$ or more, independent from the applied drug dosage. But also the tumour localization has a major impact on the cosmetic outcome. Lesions of the nose should not be treated by less than 10 J/cm$^2$ due to geometrical light distribution, light scattering, and rough surface. But the macroscopic reaction after PDT within the treatment fields was not consistent. In patients treated by the same light and drug dosages, the tumour reaction and the reaction of the adjacent normal tissue could differ, even at similar tumour locations. In one patient a complete necrosis of the whole treatment field could be observed whereas in another patient a good selective reaction, sparing the adjacent normal tissue, appeared. There might be two explanations for this effect. One reason might be the distinct skin type of the patient giving a different threshold border for the skin photosensitivity. But probably the main reason will be the differences in body weight. By relating the drug dosage to the body weight, the different drug distribution within the body compartments like fat, muscle, blood, and skin is not accounted for. As the skin is the largest organ we would suggest relating the drug dosage to the body surface, which can be calculated from body weight and body size. By this reference, a more homogeneous reaction within the drug and light dosage groups is expected. By choosing the correct drug and light combination for PDT, a selective tumour necrosis could be obtained. This accounts for the accumulation of the photosensitizer within the tumour and the clearance from the normal tissue within the 96 hours of incubation time between intravenous application of the photosensitizer and the light treatment.

Even if the results of this study are only preliminary, PDT seems to be an alternative treatment for nonmelanomateous skin tumours with an excellent cosmetic result and good response rate. PDT offers an alternative to more traditional treatments like surgery, Mohs' micrographic surgery, cryosurgery, curettage, laser ablation, or radiation therapy. Especially for patients with widespread and multiple BCC or SCC, PDT offers the advantage of treating many lesions in a single sitting.

As new portable and affordable laser systems for PDT emerge on the medical market and new photosensitizers like Foscan will become approved, PDT of various tumours will become more popular. The easy and safe method and very good cosmetic outcome for the treatment of skin tumours of the head and neck counts for this new indication of Foscan mediated PDT. By continuing this study, Foscan mediated PDT of primary nonmelanomatous skin tumours of the head and neck will probably become a new tool in substituting existing therapy concepts. The high response rate, the short term of systemic photosensitization, and the superior cosmetic outcome makes Foscan mediated PDT a safe alternative to surgical or other therapy concepts in the treatment of primary nonmelanomatous skin tumors of the head and neck.

Further studies are necessary to gain a statistical significance for the best drug and light dosage for each tumour localization and histology.

## REFERENCES

1. Boring C, Squires T, Tong T. Cancer statistics 1991. CA Cancer J Clin 1991;41:19–36.

2. Scotto J, Kopf A, Urbach F. Non-melanoma skin cancer among Caucasians in four areas of the United States. Cancer 1974;34:1333–1338.
3. Preston DS, Stern RS. Non melanoma cancer of the skin. Lancet 1992;327:1649–1662.
4. Rowe DE, Carroll RJ, Day CL. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implication for patient follow-up. J Dermatol Surg Oncol 1989;15:315–328.
5. Karagas M, Stukel T, Greenberg R, Baron J, Mott L, Stern R. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. JAMA 1992;267:3305–3310.
6. Henderson B., Dougherty T. How does Photodynamic Therapy work? Photochem Photobiol 1992;55:145–157.
7. Ochsler M. Photodynamic Therapy: the clinical perspective (Review) Arzneim Forsch/Drug Res 1997;47:1185–1194.
8. Roberts D, Cairnduff F. Photodynamic therapy of primary skin cancer: a review. Br J Plast Surg 1995;48:360–370.
9. Frazier C. Photodynamic Therapy in dermatology (review). Int J Dermatol 1996;35:312–316.
10. Fink-Puches R, Hofer A, Smolle J, Kerl H, Wolf P. Primary clinical response and long-term follow-up of solar keratosis treated with topically applied 5-aminolevulinic acid and irradiation by different wave bands of light. J Photochem Photobiol B 1997;41:145–151.
11. Jeffes EW, McCullough JL, Weinstein GD, Fergin PE, Nelson JS, Shull TF, Simpson KR, Bukaty LM, Hoffman WL, Fong NL. Photodynamic therapy of actinic keratosis with topical 5-aminolevulinic acid. A pilot dose-ranging study. Arch Dermatol 1997;133:727–732.
12. Peng Q, Warloe T, Berg K, Moan J, Kongshaug M, Giercksky KE, Nesland JM. 5-aminolevulinic acid based photodynamic therapy. Clinical research and future challenges. Cancer 1997;79:2282–2308.
13. Svanberg K, Andersson T, Killander D, Wang I, Stenram U, Andersson-Engel S, Berg R, Johansson J, Svanberg S. Photodynamic therapy of non-melanoma malignant tumours of the skin using topical δ-amino levulinic acid sensitization and laser irradiation. Br J Dermatol 1994; 130:743–751.
14. Kennedy JC. Photodynamic Therapy with endogenous protoporphyrin IX: basic principles and present clinical experiences J Photochem Photobiol B 1990;6:143–148.
15. Buchanan R, Carruth J, McKenzie, Williams S. Photodynamic Therapy in the treatment of malignant tumours of the skin and the head and neck. Eur J Surg Oncol 1989; 15:400–406.
16. Dougherty TJ. Photoradiation therapy for cutaneous and subcutaneous malignancies. J Invest Dermatol 1981;77: 122–124.
17. Gilson D, Ash A, Driver I, Feather J, Brown S. Therapeutic ratio of photodynamic therapy in the treatment of superficial tumours of skin and subcutaneous tissues in man. Br J Cancer 1988;58:665–667.
18. Gregory RO, Goldman L. Application of photodynamic therapy in plastic surgery. Lasers Surg Med 1986;6:62–66.
19. Gross D, Warner M, Schosser R. Squamous cell carcinoma of the lower lip involving a large cutaneaous surface. Photodynamic Therapy as an alternative therapy. Arch Dermatol 1990;126:1148–1150.
20. Hintschich C, Feyh J, Beyer M. Photodynamic laser therapy of basal cell carcinoma of the lid. Ger J Ophthalmol 1993;2:212–217.
21. Jones C, Mang T, Cooper M, Wilson B, Stoll H. Photodynamic therapy in the treatment of Bowen's disease. J Am Acad Dermatol 1992;27:979–982.
22. Keller G, Razum N, Doiron D. Photodynamic Therapy for non-melanomatous skin cancer. Facial Plast Surg 1989; 6:180–184.
23. Khan S, Dougherty T, Mang T. An evaluation of photodynamic therapy in the management of breast cancer. Eur J Cancer 1993;29:1686–1690.
24. Koderhold G, Jindra R, Koren H, Alth G, Schenk G. Experiences of photdynamic therapy in dermatology. J Photochem Photobiol B 1996;36:221–223.
25. McCaughan J. Photodynamic Therapy of skin and oesophgeal cancers. Cancer Invest 1990;8:407–416.
26. Pennington D, Waner M, Knox A. Photodynamic therapy for multiple skin cancers. Plast Reconstr Surg 1988;82: 1067–1071.
27. Petrelli NJ, Cebollero JA, Rodriguez-Bigas M, Mang T. Photodynamic therapy in the management of neoplasms of the perianal skin. Arch Surg 1992;27:1436–1438.
28. Robinson PJ, Carruth JAS, Fairris GM. Photodynamic therapy: a better treatment for widespread Bowen's disease. Br J Dermatol 1988;119:59–61.
29. Tse DT, Kersten RC, Andersen RL. Hematoporphyrin derivative photoradiation therapy in managing nevoid basal cell carcinoma syndrome. Arch Opthalmol 1984; 102:990–994.
30. Waldow S et al. Photodynamic therapy for the treatment of malignant cutaneous lesions. Lasers Surg Med 1987; 7:451–456.
31. Wang et al. Photodynamic therapy for 50 patients with skin cancers or premalignant lesions. Chin Med Sci J 1991;6:163–165.
32. Wilson BD, Mang T, Stoll H, Jones C, Cooper M, Dougherty T. Photodynamic therapy for the treatment of basal cell carcinoma. Arch Dermatol 1992;128:1597–1601.
33. Star WM. Light dosimetry in vivo. Phys Med Biol 1997; 42:763–787.
34. Lui H. Photodynamic therapy in dermatology with porfimer sodium and benzoporphyrin derivates: an update. Semin Oncol 1994;21:11–14.